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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,788	03/30/2001	Wei Shao	CL001207	3535

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/820,788	SHAO ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,8,9 and 24-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,8,9 and 24-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received on 12/31/03. Applicants election without traverse of group 3 is acknowledged. Claims 1-3, 5-7, and 10-23 were canceled and claims 24-30 were added as requested.

Claims 4, 8, 9, and 24-30 are pending and under consideration in this Office Action.

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains at paragraph 56 embedded hyperlinks and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). This application clearly fails to comply with the requirements of 37 C.F.R.1.821-1.825. Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final

rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **Pages 4 and 5 of Fig. 3 disclose a series of nucleic acid sequences that are not identified by SEQ ID NO.** If these sequences are listed in the current Sequence Listing, then the specification should be amended to include the appropriate SEQ ID NO in the Fig or its brief description. If these sequences are not in the current Sequence Listing, then Applicant must provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Claim Objections

Claims 8, 9, and 27-29 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous

claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 8, 9, and 27-30 are drawn to a vector comprising a nucleic acid of claim 4. However, claim 4 is drawn to an isolated nucleic acid consisting of a nucleic acid sequence. The claim uses closed language to describe the nucleic acid. As a result, claims 8, 9, and 27-29 do not further limit the isolated nucleic acid set forth in claim 4, instead, they improperly add matter which is not accounted for in claim 4, i.e. a vector. Because they do not further limit claim 4, but instead broaden it, they are improper dependent claims.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 4, 8, 9, 24, and 27-30 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either an asserted utility which is specific and substantial, or a well established utility.

The claims are drawn to isolated nucleic acid molecules consisting of a nucleic acid sequence encoding a protein comprising SEQ ID NO:2; consisting of SEQ ID NOS: 1 (cDNA) or 3 (genomic sequence); or consisting of the complements of these nucleic acids. The specification discloses that the polypeptide of SEQ ID NO:2 is related to cytochrome P450 superfamily member CYP2D6. The cytochrome P450 superfamily members are enzymes that function in detoxification and are involved in drug metabolism.

The specification discloses a variety asserted utilities for the claimed nucleic acids and the polypeptide encoded by them. At paragraph 32 the specification teaches that they can be used as models for the development of human therapeutic targets, aid in the identification of therapeutic proteins, and serve as targets for the development of human therapeutic agents that modulate drug-metabolizing enzyme activity in cells and tissues that express the drug-metabolizing enzyme. More particularly, the specification asserts utilities for SEQ ID NO:2 that are related to its activities in drug metabolism, e.g. drug screening assays. CYP2D6 is known to act on a variety of drugs (listed at paragraph 16), but the specification fails to positively identify any substrate of SEQ ID NO:2, or to assert that any particular substrate is acted on by SEQ ID NO:2. So, further experimentation would be required to determine what is the activity of SEQ ID NO:2, i.e. on what drugs it will act. Moreover, the specification does not establish any nexus between SEQ ID NOS 1-3 and any disease such that one of skill in the art could immediately use SEQ ID NOS 1-3 to develop therapy for any disease or disorder. Given this information, the use of nucleic acids for expression of SEQ ID NO:2 is not a substantial utility according to the Guidelines for Examination of Applications for Compliance With the Utility Requirement because one would have to determine the function of SEQ ID NO:2, or establish a relationship to some disease or disorder, in order to determine its real world use, if any. See MPEP 2107.01(I).

The specification also asserts that the nucleic acids of the invention can be used for a variety of purposes related to detecting, expressing, or controlling expression of SEQ ID NO:2, nucleic acids encoding SEQ ID NO:2, or alleles or orthologs of SEQ ID

NO:2. These are not substantial utilities for the reasons set forth above, i.e. further research is necessary to determine the real world use of SEQ ID NO:2 because neither its function nor any nexus between SEQ ID NO:2 and a disease or disorder has been established.

One might argue that the invention has a readily apparent utility because SEQ ID NO:2 is closely related to CYP2D6,and would be expected to act on the same substrates. SEQ ID NO:2 differs from CYP2D6 by a P34S substitution, the deletion of CYP2D6 amino acids 118-168, and M374V and T486S substitutions. See attached sequence alignment. CYP2D6 is very well characterized, and is known to act on a broad variety of substrates (see paragraph 16 of specification). However, a review of the relevant art shows that the scope of substrates accepted by CYP2D6 varies with the allele or ortholog under consideration, and that the effects of sequence changes on CYP2D6 are unpredictable in terms of substrate specificity. For example, Lewis et al (Xenobiotica 27(4): 319-340, 1997) taught that human CYP2D6 acts on debrisoquine whereas mouse CYP2D6 does not, and that human alleles include both poor metabolizer and extensive metabolizer alleles (see paragraph bridging pages 319 and 320). Also Yu et al (J. Pharm. Exp. Ther. 303(3): 1291-1300, 2002) showed that although wild type human CYP2D6 acts on codeine, the CYP2D6.10 allele does not. Furthermore, although computer generated models of CYP2D6 exist, it was recognized that predictions based on these models should be tested empirically by a variety of approaches including pharmacophore docking, chemical probe analysis, antibody binding site studies, and site directed mutagenesis. See Ellis et al (Biochem. J. 345:

565-571, 2000), paragraph bridging columns 1 and 2 on page 565. For example, although active site models indicated that S304 of CYP2D6 was a critical residue required for ligand binding, Ellis showed by site-directed mutagenesis that it was not. See abstract. Evidence that the 51 amino acid deletion would alter the activity of CYP2D6 comes from DeGroot et al (Chem. Res. Toxicol. 9:1079-1091, 1996) who developed a 3-dimensional model of CYP2D6 based on known crystal structures of bacterial cytochrome P450s. Based on this model, amino acids 118-122 of CYP2D were predicted to interact with substrates (see e.g. page 1089, column 1, last full sentence. Note that these residues are missing from SEQ ID NO:2 as they fall within the deleted region (CYPD2 118-168). Furthermore, the entire predicted C-helix, containing the conserved WXXXR motif is absent from SEQ ID NO:2. See Fig. 1 at page 1081, and page 1082, column 1, lines 7-12. Given the state of the art of predicting the activity of CYP2D6 mutations, as evidenced by Ellis above, one of skill in the art at the time of the invention could not have predicted the effects on enzyme activity of a 51 amino acid deletion that removed from the protein substrate-interacting residues as well as a highly conserved motif and an entire alpha helix. As a result one of skill in the art would have had to empirically determine if the SEQ ID NO:2 retained any activity at all, and if it did, on which substrates it would act. In other words, further research would be required to determine the real world use of the invention. Accordingly it lacks a substantial utility.

Claims 25 and 26 are not included in this rejection because, as discussed further below, they have been interpreted to embrace isolated polynucleotides that have a well established utility. See rejections under 35 USC 102 below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 8, 9, 24, and 27-30 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 8, 9, 24, and 27-30 are indefinite because it is unclear how many items were intended to be in the claim. Although the claim appears to end in a period after item "c", item "c" it is immediately followed by an item "d". Deletion of item "d" is suggested inasmuch as its limitations are present in claim 30.

Claim 24 is indefinite because it recites "the peptide" without antecedent basis.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 8, 9, 24, and 27-30 are rejected under 35 U.S.C. 112, first paragraph. Because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above under 35 U.S.C. 101, one skilled in the art would not know how to use the claimed invention.

Applicant is required to establish only a single utility which is credible, specific and substantial, or well established. In the event that the utility rejection under 35 U.S.C. 101 above is overcome, the following enablement rejection of claims 4, 8, 9, 24, and 27-30 will still apply.

Claim 4, 8, 9, 24, and 27-30 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining enablement are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

The claims are drawn to isolated nucleic acid molecules consisting of a nucleic acid sequence encoding a protein comprising SEQ ID NO:2; consisting of SEQ ID NOS:

1 or 3; or consisting of the complements of these nucleic acids. As discussed above, the specification fails to assert any specific activity of SEQ ID NO:2 or establish any nexus between SEQ ID NO:2 and any specific disease. Thus one of skill in the art would first have to determine the activity of SEQ ID NO:2, or its relationship to a disease, in order to use SEQ ID NOS: 1-3 as intended.

One might argue that such experimentation is not undue in view of the amount of information available concerning CYP2D6, a related polypeptide. SEQ ID NO:2 differs from CYP2D6 by a P34S substitution, the deletion of CYP2D6 amino acids 118-168, and M374V and T486S substitutions. See attached sequence alignment. CYP2D6 is very well characterized, and is known to act on a broad variety of substrates (see paragraph 16 of specification). However, a review of the relevant art shows that the scope of substrates accepted by CYP2D6 varies with the allele or ortholog under consideration, and that the effects of sequence changes on CYP2D6 are unpredictable in terms of substrate specificity. Lewis et al (Xenobiotica 27(4): 319-340, 1997) taught that human CYP2D6 acts on debrisoquine whereas mouse CYP2D6 does not, and that human alleles include both poor metabolizer and extensive metabolizer alleles (see paragraph bridging pages 319 and 320). Also Yu et al (J. Pharm. Exp. Ther. 303(3): 1291-1300, 2002) showed that although wild type human CYP2D6 acts on codeine, the CYP2D6.10 allele does not.

Ellis et al (Biochem. J. 345: 565-571, 2000) taught that, at the time the invention was filed, there existed in academia and the pharmaceutical industry a great interest in developing a predictive model of the active site CYP2D6, but that this was problematic

due to the absence of a crystal structure for any eukaryotic cytochrome P450, let alone a human P450. Ellis goes on to note that computer generated models of the active site of CYP2D6 needed to be validated experimentally using a variety of approaches including pharmacophore docking, chemical probe analysis, antibody binding site studies, and site directed mutagenesis. See paragraph bridging columns 1 and 2 on page 565. For example, although active site models indicated that S304 of CYP2D6 was a critical residue required for ligand binding, Ellis showed by site-directed mutagenesis that it was not. See abstract. This indicates that the state of the art of CYP2D6 structure-functional analysis was unpredictable at the time of filing, despite the existence of theoretical models of its active site. In view of the fact that one of skill in the art could not accurately predict the effect of a single amino acid substitution on the catalytic activity of CYP2D6, it is highly unlikely that one of skill in the art could predict the effect of the deletion of 51 amino acids from the polypeptide, as in SEQ ID NO: 2. It is also worth noting that Wang et al, (Drug Metab. Disp. 27(3): 385-388, 1997) taught that the P34S and T486S mutations present in SEQ ID NO:2 each decrease the activity of CYP2D6 (see second sentence of paragraph bridging columns 1 and 2 on page 385). So, SEQ ID NO:2 represents a polypeptide comprising 2 mutations with a negative effect on activity, combined with a 51 amino acid deletion (representing about 10% of CYP2D6).

Evidence that the 51 amino acid deletion would alter the activity of CYP2D6 comes from DeGroot et al (Chem. Res. Toxicol. 9:1079-1091, 1996) who developed a 3-dimensional model of CYP2D6 based on known crystal structures of bacterial

cytochrome P450s. Based on this model, amino acids 118-122 of CYP2D were predicted to interact with substrates (see e.g. page 1089, column 1, last full sentence. Note that these residues are missing from SEQ ID NO:2 as they fall within the deleted region (CYPD2 118-168). Furthermore, the entire predicted C-helix, containing the conserved WXXXR motif is absent from SEQ ID NO:2. See Fig. 1 at page 1081, and page 1082, column 1, lines 7-12.

Given the state of the art of predicting the activity of CYP2D6 mutations, as discussed above, one of skill in the art at the time of the invention could not have predicted the effects on enzyme activity of combining two deleterious mutations (P34S and T486S) with a 51 amino acid deletion that removed from the protein substrate-interacting residues as well as a highly conserved motif and an entire alpha helix. As a result one of skill in the art would have had to empirically determine if the SEQ ID NO:2 retained any activity at all, and if it did, on which substrates it would act. One might argue that this would be a simple matter of assaying the known CYP2D substrates. However, as discussed above the effects of a 51 amino acid deletion, including active site residues, are unpredictable with respect to substrate specificity. As set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to **known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. In this case, the specification fails to positively identify a single substrate of SEQ ID NO:2, and fails to establish any nexus between SEQ ID NO:2 and any disease or disorder. Absent such guidance or working examples in the specification, in view of the state of the art and the unpredictable nature of the subject matter, even those of the highest level the level of skill in the art would have to perform undue experimentation in order to use SEQ ID NOS: 1-3 as intended.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US Patent 5,474,796, issued 12/12/95).

Claims 25 and 26 are drawn to "an isolated polynucleotide consisting of a nucleotide sequence set forth in" SEQ ID NO:1 (claim 25) or SEQ ID NO: 3 (claim 26). The phrase "a nucleotide sequence" has been interpreted to mean "any nucleotide sequence", so the claims read on any isolated polynucleotide consisting of any nucleotide sequence found in SEQ ID NOS: 1 or 3, including fragments of SEQ IDNOS: 1 or 3. It is apparent from paragraphs 169 and 170 that the invention embraces oligonucleotides on a microarray chip. The last sentence of paragraph 170 states that the [p]olynucleotides used in the microarray or detection kit may be oligonucleotides.

Brennan teaches an array of isolated oligonucleotides comprising every conceivable 10mer oligonucleotide sequence. See column 9, lines 48-55. Thus Brennan teaches every 10 nucleotide fragment of SEQ ID NOS: 1 and 3, and anticipates the claims. This rejection can be overcome by substituting "the" for "a" in the phrase "a nucleotide sequence". However, such an amendment would necessitate a new ground of rejection under 35 USC sections 101 and 112, first paragraph as set forth for claims 4, 8, 9, 24, and 27-30 above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.